REMARKS

The applicants' representative would like the thank the examiner for time taken on July 30, 2009 to discuss issues outstanding in this matter.

Reconsideration is respectfully requested in view of the amendment and remarks made herein.

Amendment to the claims

Please cancel all pending claims and enter new claims 76 through 93. All new claims find support in the canceled claims as set out in the claim chart in attached Appendix A.

The amendment includes no new matter.

The amendment is made without prejudice to the applicants' right to pursue claims of the same or similar subject matter in a duly filed continuing application.

The objections to the claims

All previous objections to the claims are obviated by submission of new claims in this paper. Specifically, the assertedly improper dependency and superfluous punctuation have been corrected and the objections may be withdrawn.

The Rejection under 35 USC §112, first paragraph

Claims 48, 49, 50, 55, 56, 59 through 68, 70, 71, 73, 74, and 75 were rejected under 35 USC 112, first paragraph, for assertedly lacking written description in the specification. In the office action, the basis for rejection has repeated in part as set out in previous office actions. For the first time, however, the examiner has added an additional basis for the rejection, alleging that "claim 55 does not establish whether the native protamine used as a comparison is mammalian or other organism." [page 7 of the office action] Along this line the examiner added that "[n]o identified source as to where the protamine is derived from is provided in the claim to guide one or ordinary skill in the art to determine where the recited fragment is from and the composition of amino acids. [page 7 of the office action]

To assertedly further support the rejection, the examiner referred to Vilfan describing mammalian protamine domains [page 7 of the office action] and then stated that while claim 74 is directed to a fragment comprising five or six arginines and one proline,

"there are protamines reported in the art that do not have a proline or glycine." [page 7] Further, "claim 72 recites the fragment is a protease cleavage product and lists [proteases] which would produce different fragments based on cleavage sites." [page 7 of the office action] Chang was cited for disclosing an octapeptide tested to neutralize heparin. [page 7] The examiner continued stating, "[m]oreover, the instant specification provides several reasons why thermolysin would not be a preferred method of cleavage" [page 7] and added that without structure-function correlation, the worker of ordinary skill in the could not conclude that applicants were in possession of the genus of fragments encompassed by the claims." [page 7] The examiner also repeated a previously stated position that claim 67 recites a first and a second protamine which means there can be more than one fragment. [page 7] and that claim 63 recites an undefined coagulant. [page 8]

The examiner further made reference again Tam [page 8 of the office action] for the proposition that administration of protamine "can trigger a catastrophic reaction is some patients," and continued by asserting that claim 74 and 75 recite 5 or 6 arginines and even 1 proline, giving a molecular weight of 1159 daltons, "and it is unclear what other residues would be encompassed in the structure to make up the remaining weight in the protein structure to achieve the recited '2500 Daltons" absent guidance. [page 8 of the office action] Reference again was made to discussion of adequate written description for a biomolecule sequence in MPEP 2163 [page 8 of the office action], and the examiner concluded repeating the previous references to court decisions in *Vas-Cath* and *Fiers*.

The applicants respectfully traverse, submitting that the application as filed demonstrates that the applicants were in possession of the invention as claimed as required by *Vas-Cath*. The applicant further submits that the examiner has purportedly based the rejection, in part, on grounds that do not apply to an analysis of adequate written description, and in part, on misinterpretation of appropriate case law.

In the first instance, the examiner's citation of the disclosure in Tam for the proposition that administration of protamine can have catastrophic effects on a patient is irrelevant to the question of whether the written description requirement is met. The question is whether the applicant was in possession of the claimed invention, regardless of if the invention leads to adverse side effects or not. The consequences, good or bad, of a method of treatment are appropriately addressed by the Food and Drug Administration.

In the second instance, regarding the examiner's apparent requirement that the entire amino acid sequence of the recited protamine be in the claim, the applicants submit that case law does not have such a high standard. In setting out the rejection, the examiner relied on the Federal Circuit decision in *Regents of the University of California v. Eli Lilly*, quoting,

> A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus . . . .").

The applicants submit as a first and minor point in rebuttal that the holding in *Lilly* relates to heretofore unknown DNA (as opposed to well know and well characterized protamine amino acids sequences) and as a second and more significant point, that the holding in *Lilly* does not require the precise and complete polynucleotide structure of even the unknown DNA at issue in that case.

> In *Lilly*, the court relied on the holding in *Fiers* stating, .
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, **or** physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." [*Regents of the University of California v. Eli Lilly*], at 1170, 25 USPQ2d at 1606. [Emphasis added]

Literal reading of this holding makes it clear that there are alternatives to a molecule's structure that can satisfy the written description requirement and the applicants have made this point on several occasions, i.e., that physical properties of the protamine at issue are recited in even the broadest claim, and in certain claims, additional structural features and

even restriction digests are recited. The applicants representative discussed this point with the examiner in the telephone call on July 30.

That said and in order to expedite prosecution that has dragged for quite some time without resolution, the applicants have amended the new claims, and specifically the single independent claim 76, to recite that the method utilized a modified protamine with the following physical properties:

- the protamine is a fragment,

- the fragment is a protease cleavage product,

- the fragment comprises a minimum of six arginine amino acid residues, and

- the fragment has a molecular weight of between about 400 and about 2500 Daltons as determined by gel filtration.

With this amendment, the applicants submit that more than a threshold characterization of the recited protamine is provided.

Inasmuch as analysis of adequate written description is an analysis of what is claimed in view of what is described in the specification, the applicants emphasize the detail with which the specification supports a finding that the applicants were in possession of what is claimed.

In the published application at paragraph 103, the specification provide sources of protamines.

> 0103] Protamine consists of a group of heterogeneous polycationic peptides with an average molecular weight of about 4500 daltons. Protamine is found in sperm and in fertilized eggs from a variety of sources, including, but not limited to, mammals, amphibians and fish, with salmon and herring being the most common source. However, protamine has also been isolated from fertilized amphibian eggs (U.S. Pat. No. 5,187,260). Protamine from any of these sources is contemplated for use in the preparation of the instant LMWP compositions.

Paragraphs 104 and 105 then follow with extensive detail for exemplified embodiments. Table 1 referenced in paragraph 104 provide complete detail about the amino acid content of these specific.

With regard to the examiner's comment at page 10 of the office action that a structure-function relationship is needed to describe an operative protamine fragment, attention is directed to the specific example. For example, paragraph 153 discloses,

> [0153] The individual fractions of the thermolysin-digested protamine seen in FIG. 1 were collected and tested for ability to neutralize heparin using the same sensor method. FIG. 3 illustrates the relationship between the degree of heparin neutralization (assuming a 100% neutralization for untreated protamine) and the molecular weight of LMWP fragments. The degree of heparin neutralization increased with the increasing molecular weight of LMWP and reached a plateau (100% neutralization) after a molecular weight of approximately 1,100 daltons (FIG. 3). These results suggest that the LMWP fragments with a molecular weight as low as 1.1 kDa still retain their full ability of heparin neutralization.

This disclosure teaches a physical property of an exemplified embodiment that is necessary for function.

Regarding structure, the specification teaches at paragraphs 154 and 155,

> This "pooled fraction" was not homogeneous and contained at least 3 to 4 LMWP fragments as resolved by reverse-phase chromatography. This finding was somewhat anticipated considering the heterogeneous nature of protamine even prior to its proteolytic digestion. The amino acid analysis of this pooled fraction revealed a composition of 5-6 arginine, 1 proline, 1 serine, and I alanine residues, along with trace amounts of threonine, valine, and glycine residues. These results are in good agreement with those reported by other investigators for thermolysin-treated protamine fragments with similar molecular weights (Ando et al., 1973).
>
> [0155] These studies suggest that six arginine residues will be the minimum requirement of LMWP for complete neutralization of heparin activity. This conclusion is consistent with literature findings on the binding of heparin with ATIII (Smith and Kanuer, 1987; Cardin and Weintraub, 1989). Both the experimental results (Smith and Kanuer, 1987) and theoretical prediction (Cardin and Weintraub, 1989) suggest that a sequence containing at least 4 to 5 basic amino acid residues is required for ATIII to bind effectively with heparin. It is therefore reasonable to assume that more than five arginine residues are required for LMWP to neutralize heparin, especially since neutralization necessitates a stronger binding to heparin than that of ATIII in order to displace ATIII from heparin.

Thus, a structural contribution to function is described for exemplified embodiments.

Regarding the immunological limitation of the method, paragraph 159 discloses,

> The antigenicity of LMWP, which is defined as its ability to be recognized by anti-protamine antibodies, was also examined by utilizing the same ELISA method but by using a LMWP-coated microplate for antibody detection in protamine-immunized mice. As shown by the open bars in FIG. 7, anti-protamine antibodies exhibited extremely low level of cross-reactivity, if any at all, towards LMWP, with the absorbance readings less than one-tenth for

> LMWP when compared to those for protamine. These studies confirm that LMWP derived from protamine with a molecular weight of approximately 1,200 daltons is markedly devoid of its immunological properties.

Here one has to conclude that a physical property is taught to contribute to yet another recited limitation in the claims.

One cannot conclude, however, that these specific disclosures are critical to the invention and therefore must be recited *in ipsis verbis*. For example, the statement that "the LMWP fragments with a molecular weight as low as 1.1 kDa still retain their full ability of heparin neutralization" cited above does not imply that a smaller fragment will not have the ability to neutralize heparin. For this embodiment, at least a 1.1 kDa is required for *full* neutralizing property. Similarly, the statement that "LMWP derived from protamine with a molecular weight of approximately 1,200 daltons is markedly devoid of its immunological properties" does not mean that a smaller or larger fragment will not be devoid of the tested immunological property tested. It simply teaches that for this embodiment, the reduced immunogenicity is *marked* devoid, not that it is not reduced with any other fragments.

Thus, in view of the detailed teaching of the application, the applicants submit that the specification fully supports the full scope of the invention as claimed and therefore requests that the rejection for asserted lack of written description be withdrawn.

CONCLUSION

In view of the amendment and remarks made herein, the applicants believe that all claims are in condition for allowance and respectfully request notification of the same,

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Respectfully submitted,

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APPENDIX A

76 (New) A method of inactivating heparin or low molecular weight heparin, comprising contacting heparin or low molecular weight heparin with a composition comprising an amount of at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin; wherein said purified protamine fragment is a protease cleavage product, comprises a minimum of six arginine amino acid residues, is bioactive, has a molecular weight of between about 400 and about 2500 Daltons as determined by gel filtration and has reduced immunoresponsiveness or toxicity compared to native protamine.	55. (Canceled) A method of inactivating heparin or low molecular weight heparin, comprising contacting heparin or low molecular weight heparin with a composition comprising an amount of at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin; wherein said purified protamine fragment is bioactive, has a molecular weight of between about 400 and about 2500 Daltons as determined by gel filtration and has reduced immunoresponsiveness or toxicity compared to native protamine. 71. (Canceled) The method of claim 55 wherein the protamine fragment is a protease cleavage product.
77. (New) The method of claim 76, wherein said purified protamine fragment has a molecular weight of between about 400 and about 2000 Daltons.	48. (Canceled) The method of claim 55, wherein said purified protamine fragment has a molecular weight of between about 400 and about 2000 Daltons.
78. (New) The method of claim 77, wherein said purified protamine fragment has a molecular weight of between about 500 and about 1350 Daltons.	49. (Canceled) The method of claim 48, wherein said purified protamine fragment has a molecular weight of between about 500 and about 1350 Daltons.

79. (New) The method of claim 77, wherein said purified protamine fragment has a molecular weight of between about 1100 and about 1300 Daltons.	50. (Canceled) The method of claim 48, wherein said purified protamine fragment has a molecular weight of between about 1100 and about 1300 Daltons.
80. (New) The method of claim 76, wherein said heparin or low molecular weight heparin is located within a mammal and said composition is administered to said mammal.	56. (Canceled) The method of claim 55, wherein said heparin or low molecular weight heparin is located within a mammal and said composition is administered to said mammal.
81. (New) The method of claim 80, wherein said mammal exhibits excessive bleeding associated with systemic heparinization.	59. (Canceled) The method of claim 64, wherein said mammal exhibits excessive bleeding associated with systemic heparinization.
82. (New) The method of claim 80, wherein said mammal exhibits excessive bleeding associated with extracorporeal blood circulation.	60. (Canceled) The method of claim 64, wherein said mammal exhibits excessive bleeding associated with extracorporeal blood circulation.
83. (New) The method of claim 80, wherein said mammal exhibits excessive bleeding associated with a disease or disorder.	61. (Canceled) The method of claim 64, wherein said mammal exhibits excessive bleeding associated with a disease or disorder.
84. (New) The method of claim 80, wherein said mammal exhibits excessive bleeding associated with a trauma or surgery.	62. (Canceled) The method of claim 64, wherein said mammal exhibits excessive bleeding associated with a trauma or surgery.
85. (New) The method of claim 80 further comprising administering a coagulant to said mammal.	63. (Canceled) The method of claim 64 further comprising administering a coagulant to said mammal.

86. (New) The method of claim 80, wherein said mammal has or is at risk for developing excessive bleeding.	64. (Canceled) The method of claim 56, wherein said mammal has or is at risk for developing excessive bleeding.
87. (New) The method claim 77, wherein said purified protamine fragment has a molecular weight of about 1300 Daltons.	65. (Canceled) The method claim 48, wherein said purified protamine fragment has a molecular weight of about 1300 Daltons.
88. (New) The method of claim 77, wherein said purified protamine fragment has a molecular weight of about 1200 Daltons.	66. (Canceled) The method of claim 48, wherein said purified protamine fragment has a molecular weight of about 1200 Daltons.
89. (New) The method of claim 76, wherein said composition comprises at least a first and at least a second purified protamine fragment.	67. (Canceled) The method of claim 55, wherein said composition comprises at least a first and at least a second purified protamine fragment.
90. (New) The method of claim 80, wherein said mammal is a human subject.	68. (Canceled) The method of claim 56, wherein said mammal is a human subject.
91. (New) The method of claim 76 wherein inactivating heparin or low molecular weight heparin treats or prevents undue or excessive bleeding in a mammal.	70. (Canceled) The method of claim 55 wherein inactivating heparin or low molecular weight heparin treats or prevents undue or excessive bleeding in a mammal.
92. (New) The method of claim 76 wherein the protamine fragment is a protease cleavage product and said protease is selected from the group consisting of thermolysin, ficin, collagenase, kallikrein and proline-specific endopeptidase.	72. (Canceled) The method of claim 70 wherein the protamine fragment is a protease cleavage product and said protease is selected from the group consisting of thermolysin, ficin, collagenase, kallikrein and proline-specific endopeptidase.

93. (New) The method of claim 76 wherein the protamine fragment is derived from a protamine selected from the group consisting of salmon protamine and clupeine protamine.	73. (Canceled) The method of claim 55 wherein the protamine fragment is derived from a protamine selected from the group consisting of salmon protamine and clupeine protamine.